PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 4

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
0099326-wsgs		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06211	04/07/2000	12/07/1999
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant MERCK PATENT GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/01/2001	02.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Perez, C Telephone No. +49 89 2399 2484

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06211

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-32 as originally filed

Claims, No.:

1-11 as originally filed

Sequence listing part of the description, pages:

37-45, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-3, 5, 9-10
	No:	Claims	1,4, 6-8, 11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

1. **Additional remark to item I (basis of opinion)**

A "Sequence Listing" has been filed with the present application. This "Sequence Listing" comprises SEQ ID N°1 to SEQ N°6 (p.7-45).

2. **Additional remark to item II (priority)**

The priority claimed for the present application has been found to be valid. Thus, the P-documents cited in the international search report are mentioned herein in the manner provided for in Rule 70.10, because they may nevertheless be anticipating the novelty of the claims during the regional phase examination (see § 4).

3. **Additional remarks to item V (reasoned statement under Rule 66.2(a) (ii) with regard to novelty, inventive step or industrial applicability)**

3.1 Present application

The present application discloses the cloning of a serine protease, herein denominated Seripancrin, which is specifically surexpressed in certain tumours. In particular, it discloses the nucleic and deduced amino acid sequences encoding the main splicing isoform of Seripancrin, SEQ ID N°1 and 2 respectively. Said protein is also characterized by a molecular weight of 55 kDa by SDS PAGE analysis, and a pI of 5.7. The gene encoding Seripancrin maps to chromosome 11q22-q23.

3.2 Prior art documents

The following documents are considered to be relevant for assessing the novelty and inventiveness of the claimed subject-matter:

D1: JP-09149790

D2: Genes Chromosomes Cancer, 1997, vol.19, N°2, Gress et al., p.97-103

D2, cited in the specifications, has come to the attention of the IPEA during examination. A copy is enclosed herein.

(i) **D1**, a japanese application, was cited by the applicant in the specifications.

D1 discloses the cloning and characterization of serine proteases derived from a human colon carcinoma cell COLO 201, herein denominated SP59, SP60 and SP67. In particular, D1 provides the nucleotide (699 nucleotides) and amino acid (233 amino acids) sequences of SP60 (SEQ ID N°4 in D1). The nucleotide SP60 sequence displays an 100 % identity in 699 nucleotides overlap with SEQ ID N°1 of the present application, and its amino acid sequence displays an 100 % identity in

233 amino acid overlap with SEQ ID N°2 of the present application. Also disclosed are a recombinant vector comprising said DNA molecule (D1: claim 3) , host cell transformed with said vector (D1: claim 4) to produce said recombinant SP60, as well as a method for screening an inhibitor of said protease (D1: claim 7).

(ii) **D2** discloses the isolation of stretches of cDNA overexpressed in pancreas tumour.

3.3 Statement with regard to novelty and inventive step (Articles 33(2)and (3) PCT)

3.31 Claims 1, 4, 6-8 and 11

The subject-matter of claims 1, 4, 6-8 and 11 does not meet the requirements of Articles 33(2) and (3) PCT, because said claims lack novelty in view of D1 and/or their lack of clarity (see § 5).

i) Since the SP60 nucleotide and amino acid sequences disclosed in D1 display an 100 % identity with SEQ ID N°1 and 2 of the present application respectively (see § 2.2 i), D1 is detrimental to novelty of **claims 1, 4, 6-8 and 11**.

ii) **Claims 1 and 4** also lack novelty, because of the lack of clarity of the expressions "fragment" and "variant" used in said claims (see § 5.2). Actually, any DNA/polypeptide may be considered as a variant from any other DNA/polypeptide.

3.32 Claims 1-11

The subject-matter of claims 1-11 does not meet the requirements of Article 33 (3) PCT, because said claims do not involve an inventive step in view of the teachings of D1 and D2, and common knowledge of the person skilled in the art.

The attention of the applicant is drawn to the fact that claims 1-11 do not involve an inventive step, even if the applicant overcomes the above novelty objection by restricting the scope of claims 1 and 4 to claims 2-3 and 5.

i) D1 is considered to be the closest prior art, because it discloses the nucleotide and amino acid sequences encoding a serine protease, SP60, isolated from a human colon carcinoma useful for cancer diagnosis and screening of therapeutic compounds. Thus, the technical problem faced by the present application is to provide an alternative serine protease and its encoding cDNA for use in cancer

diagnosis and therapy. The solution provided by the present application is a polynucleotide comprising the SEQ ID N°1 or encoding the polypeptide of SEQ ID N°2.

However, the cloning of a full length cDNA encoding a protein using a known partial cDNA, such as the cDNA provided in D1, as a probe can be performed in a straightforward manner without the requirement of any inventive skill. Actually, the applicant himself wrote within the specifications that he uses nothing more than standard methods to clone said Seripancrin gene. Consequently, it would have been obvious, for the person skilled in the art, looking for a solution to the above problem, to try, with a high expectation of success, to isolate an homologue of D1 serine protease within the D2 pancreatic cancer cDNA library using D1 SP60 polynucleotide as a probe. By doing so, he would inevitably isolate the main splicing isoform of Seripancrin claimed in the present application, since the other isoforms do not exhibit any homology to SP60 polynucleotide sequence. Thus, the solution provided by the present application does not involve any inventive activity.

Furthermore, since the partial sequence of the claimed Seripancrin disclosed in D1 already solves the problem of the invention, the IPEA considers that any extension of said sequence, such as the Seripancrin sequence provided by the present application, does not involve an inventive step, unless the applicant is able to show that the claimed enzyme exhibits surprising or unexpected effect over the serine protease SP60 disclosed in D1. Consequently, the subject-matter of claims 1-8 does not involve an inventive step in view of the teachings of D1, combined with D2 and common knowledge of the person skilled in molecular biology and biochemical methods.

ii) Techniques for obtaining antibodies are well-known in the art. Thus, antibodies can be obtained against any known peptide in a straightforward manner, without involving any inventive skill. Accordingly, the provision of antibodies against antigens that lack novelty and/or inventiveness, such as the polypeptide of present claim 1, cannot be regarded as inventive. Therefore, **claim 10** lacks an inventive step.

The same argumentation holds true for the generation of fusion protein. In fact, the Immunoglobulin Fc region is one of the common polypeptide domain used to prepare fusion protein suitable for high-throughput screening assays (see the litterature cited in the specifications). Thus, the inventiveness of **claim 9** cannot be acknowledged.

iii) Furthermore, the use of an enzyme for evaluating compounds with stimulation or inhibition activity can only be considered as inventive, if said enzyme is novel and inventive, or if the claimed method exhibits other essential features over the methods disclosed in the prior art. Since the polypeptide of claim 1 is the only essential feature of claim 1, and since said polypeptide is not new and not inventive over the serine protease known in the art (see § 3.31 and 3.32 i), the inventiveness of **claim 11** cannot be acknowledged.

4. Additional remark to item VI (certain published documents, Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO9936550	**22.07.1999**	**12.01.1999**	**16.01.1998**
WO0012758	**09.03.2000**	**01.09.1999**	**02.09.1998**
WO0012708	**09.03.2000**	**01.09.1999**	**01.09.1998**

WO-A-9936550 discloses the cloning of a human serine protease associated with cancer, herein denominated HUPM-6. The nucleotide sequence encoding said enzyme displays a 99.923 % identity with the claimed SEQ ID N°1 over its entire sequence. The identity at the amino acid level is 99,77 % over the entire length of SEQ ID N°2.

Similarly, **WO-A-0012758** discloses the cloning of a cancer specific gene (CSG) sequence, which displays 99.923 % identity with the claimed SEQ ID N°1 over its entire length.

Finally, **WO-A-0012708** reports the cloning of human PRO1570 characterized by its sequence SEQ ID N°274. Said nucleotide sequence displays a 100 % identity in 859 nucleotides overlap with the claimed SEQ ID N°1. Said amino sequence displays a 98,848 % identity in 434 amino acids overlap with the claimed SEQ ID N°2.